A CELL-SHEET-FRAGMENT BASED APPROACH FOR DELIVERY OF AUTOLOGOUS BONE MARROW-DERIVED MESENCHYMAL STEM CELLS FOR CELLULAR CARDIOMYOPLASTY IN A PORCINE MODEL

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INTRODUCTION

Cellular cardiomyoplasty is a promising therapy for patients with myocardial infarction (MI) [1]. Among the cell types studied, mesenchymal stem cells (MSCs) are regarded as the most practical cell source for clinical applications, as they can be readily isolated from the patients' bone marrows. However, current procedures for cell transplantation through direct injection of trypsin-dissociated cells are frequently associated with a low retention rate of engrafted cells and a suboptimal consequence of cell survival and function [2]. To address this concern, a method employing a thermo-responsive methylcellulose (MC) hydrogel system, for the fabrication of cell sheet fragments of MSCs without applying proteolytic enzymes, was previously reported by our group [3]. Our results demonstrated that the harvested MSC sheet fragments retained endogenous extracellular matrix and offered a significantly higher cell retention rate following engraftment in a rat model, thus showing a better functional benefit for the infarcted heart when compared with dissociated MSCs [4]. In this study, a porcine model with surgically induced MI was used to evaluate the effectiveness of engraftment of cell sheet fragments of autologous bone marrow-derived MSCs on its post-infarcted cardiac function. Swine have been considered as an ideal large animal model for the clinical translation of cardiovascular research, due to their resemblance to human organ size and physiology. These translational studies in large animal models are necessary if the tremendous potential suggested by rat studies is to be realized clinically.

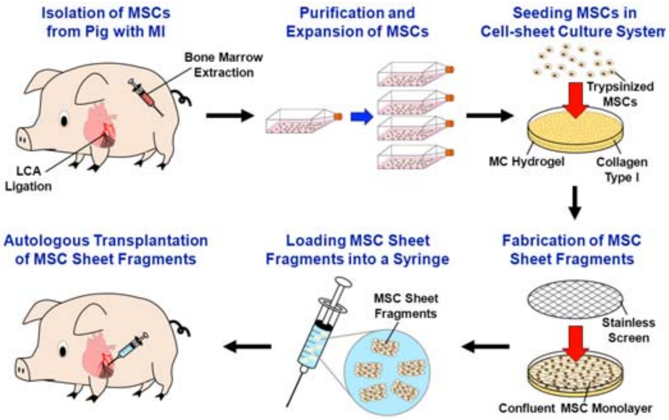

Figure 1. Schematic illustration of the processes used for the fabrication of cell sheet fragments of bone marrow-derived MSCs for autologous cellular cardiomyoplasty.

EXPERIMENTAL METHODS

Each pig was subjected to surgically induced MI, and its bone marrow was extracted simultaneously. The MSCs were then isolated, amplified and seeded on the surface of MC hydrogel system. After reaching confluence, a sterilized stainless screen was used to compress and fragment the grown MSC monolayer, resulting in fragmented MSC sheets. Finally, the obtained MSC sheet fragments were collected for autologous intramyocardial transplantation (Fig. 1). The groups treated with saline or dissociated MSCs were used as controls. Cardiac functions were evaluated by echocardiography before MI, at 4 weeks after MI induction and at 4 weeks post cell transplantation. Finally, animals were sacrificed, and the hearts were retrieved and processed for histological assessment.

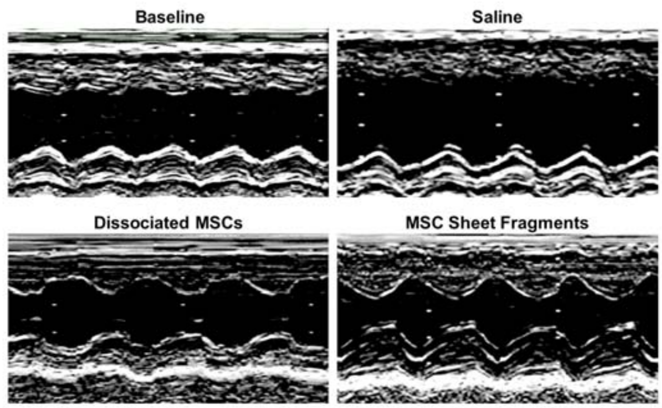

Figure 2. Representative traces of LV short-axis M-mode echocardiograms obtained at baseline (at 4 weeks after MI induction) and at 4 weeks after treatment.

RESULTS AND DISCUSSION

As indicated by the M-mode echocardiograms shown in Fig. 2, the dilation of left ventricle (LV) was significantly attenuated in the heart that received MSC sheet fragments when compared to the hearts treated with saline or dissociated MSCs (control groups).

Figure 3. Representative histological cross-sections that depicting the infarct zones of the hearts for all studied groups at 4 weeks after treatment.

Gross pathologic examination revealed that the heart that received saline treatment exhibited severely transmural infarction with significantly anterior wall thinning and LV chamber enlargement (Fig. 3). Conversely, transplantation of MSC sheet fragments substantially reduced the ratio of LV occupied by fibrotic scar tissues, maintained LV wall thickness and prevented the global cardiac morphology from post-infarcted dilation.

CONCLUSION

These results suggest that transplantation of MSC sheet fragments in infarcted hearts can markedly attenuate the adverse ventricular dilation, preserving the cardiac function post MI, thus supporting the hypothesis that our approach holds promise to become a translational applicable strategy for autologous stem cell-based cardiac repair.

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